Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

# Gut-brain axis hypothesis of Parkinson‘s disease
# Ufa, May 28th, 2020

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# PD Progression



**Olfactory loss**
**RBD, constipation**
**anxiety,**
**depression**

**Bradykinesia,**
**Rigidity,**
**Rest-tremor,**
**(+/- non-motor-symptoms)**

**Motor complications:**
**Wearing off/dyskinesias,**
**gait and balance problems,**
**axial deformities,**
**dysarthria/dysphagia**

**Non-motor symptoms:**
**cognitive decline/**
**dementia, psychosis,**
**autonomic dysfunction,**
**sleep–wake-dysregulation**

**Gene mutations,**
**alpha-synuclein levels,**
**imaging abnormalities**

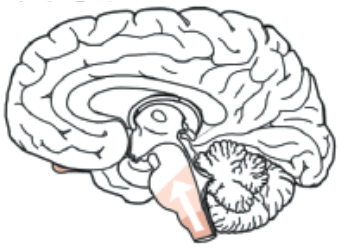
*Pre-symptomatic PD* *Pre-Motor PD* *Early PD* *Moderate PD (stable)* *Advanced PD*

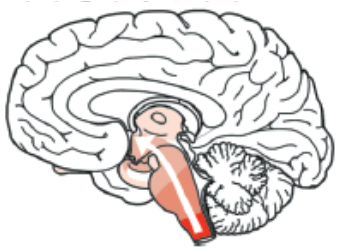
-10y -6y 0 2y 5y 10y 15y

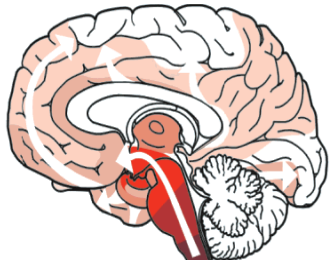
**Onset of clinical PD premotor phenotype**

**Onset of clinical PD motor phenotype**

**Diagnosis**







# GI-Tract: Window or Entry Zone



## Frequency of bowel movements and the future risk of Parkinson's disease

R.D. Abbott, PhD; H. Petrovitch, MD; L.R. White, MD; K.H. Masaki, MD; C.M. Tanner, MD, PhD; J.D. Curb, MD; A. Grandinetti, PhD; P.L. Blanchette, MD; J.S. Popper, MD; and G.W. Ross, MD

NEUROLOGY 2001;57:456–462

**Frequency of bowel movements in 6790 men between 1971 and 1974**

- **Follow up for incident PD for 24 yrs**
- **69 PD with average time to onset 12 yrs**

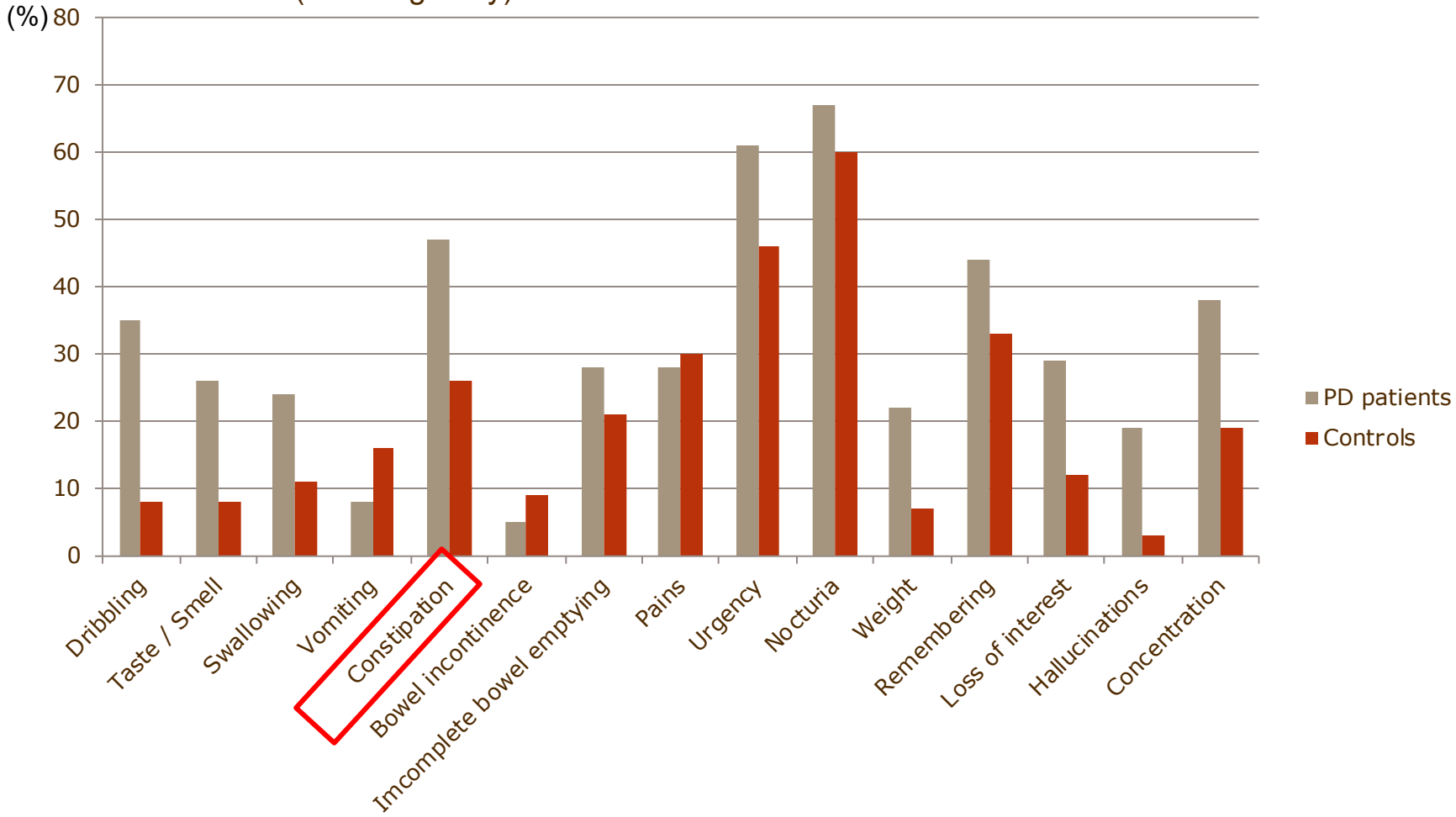
- **18,9/ 10.000 person years in men <1 bowel movement/ day**
- **3,8 / 10.000 person years in men >2 bowel movements/ day**

- **Constipation as a marker of early PD or susceptibility or environmental factors that may cause PD.**

# NMS in PD in comparison with an age-matched control group



- NMSQuest study: Non-motor questionnaire for PD patients
  - 123 PD patients (mean age 68y, disease duration 6.4y, H&Y 2.5)
  - 96 controls (mean age 65y)

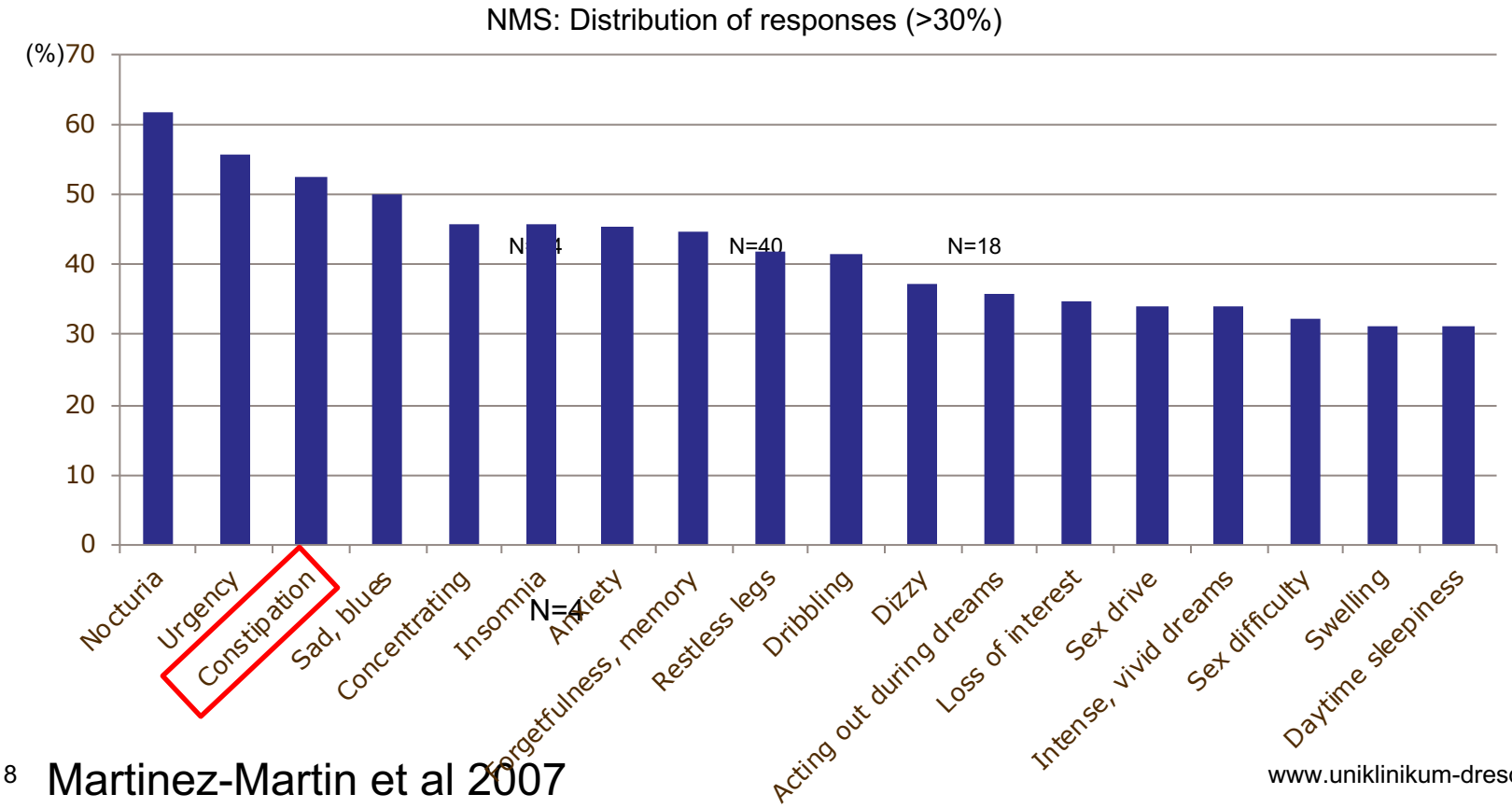



Chaudhuri & Odin 2010; Chaudhuri et al 2006

# Prevalence of Nonmotor Symptoms in Parkinson's Disease: Study Using Nonmotor Symptoms Questionnaire



- Observational, multicenter, international, cross-sectional study
  - 545 PD patients completed the revised NMSQuest
  - Mean age 68y, disease duration 7y, H&Y 2.5
  - Mean number of NMS per patient (NMSQ-T): 10.3




Martinez-Martin et al 2007

# GIT manifestations in the pre-motor phase



J Neurol (2013) 260:1332–1338
DOI 10.1007/s00415-012-6801-2

ORIGINAL COMMUNICATION

## Gastrointestinal manifestations in Parkinson's disease: prevalence and occurrence before motor symptoms

Maria G. Cersosimo · Gabriela B. Raina · Cristina Pecci · Alejandro Pellene · Cristian R. Calandra · Cristiam Gutiérrez · Federico E. Micheli · Eduardo E. Benarroch

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# Pre-motor signs



**Table 3** Gastrointestinal manifestations with onset before motor symptoms in Parkinson's disease patients with a disease duration no longer than 5 years ($n = 72$)

| GIS (n) | Onset before motor symptoms | | | |
|---|---|---|---|---|
| | *n* (%) | Always present[a] | Not always present | |
| | | | *n* (%) | Years before the onset of MS (mean ± SD, range) |
| Dry mouth (39) | 8 (20.5) | 0 | 8 | 5.2 ± 4.5 (1–10) |
| Drooling (24) | 0 | – | – | – |
| Dysphagia (13) | 0 | – | – | – |
| Heartburn (25) | 16 (64) | 7 (43.7) | 9 (56.2) | 6.1 ± 6.2 (1–17) |
| Bloating and satiety (35) | 23 (65.7) | 16 (69.5) | 7 (30.4) | 11.5 ± 6.5 (3–18) |
| Nausea (10) | 0 | – | – | – |
| Constipation (31) | 27 (87) | 16 (59.2) | 11 (40.7) | 4 ± 4.6 (1–13) |
| Defecatory dysfunction (39) | 23 (58.9) | 17 (73.9) | 6 (26) | 3.7 ± 2.7 (1–7) |

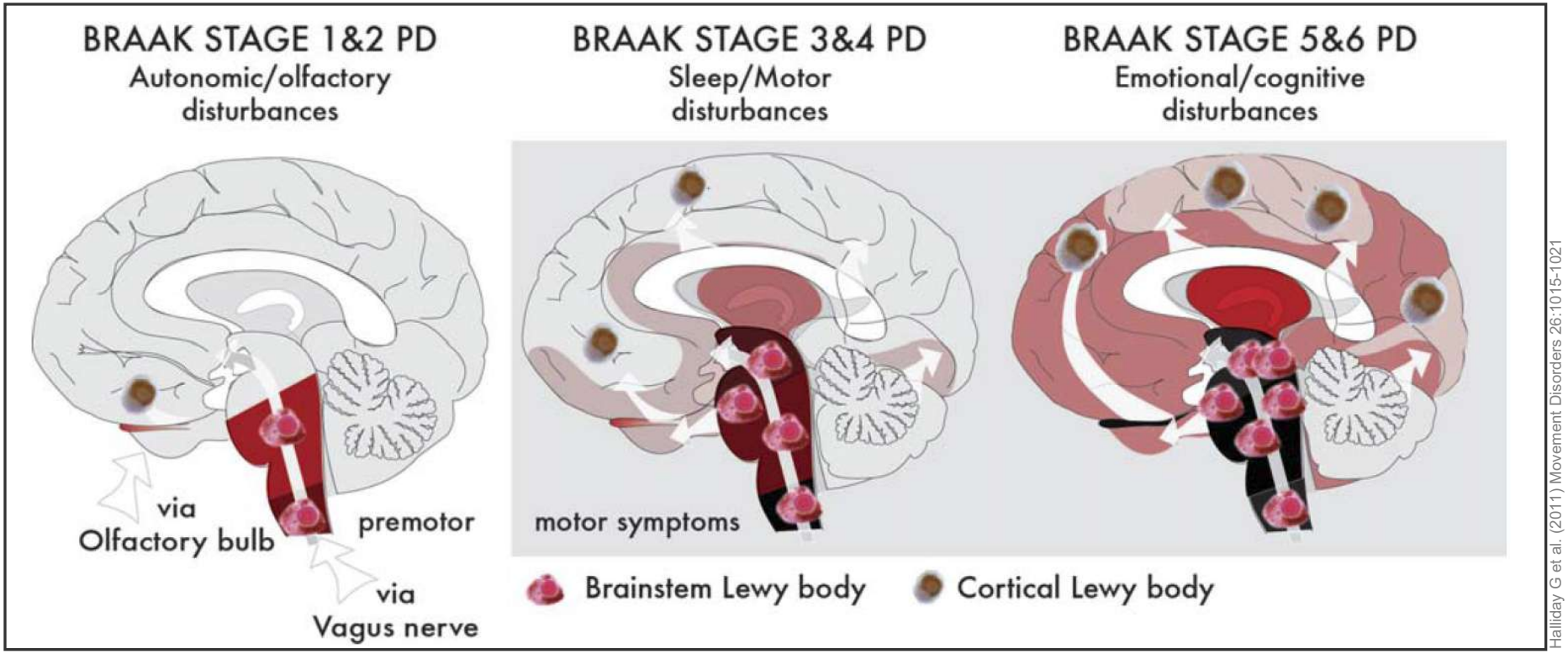
*MS* motor symptoms, *GIS* gastrointestinal symptoms

[a] Symptoms reported as lifelong problems

Cersosimo MG et al. (2013) J Neurol 260:1332-1338

# The Braak Stages






Halliday G et al. (2011) Movement Disorders 26:1015-1021

**FIG. 1.** Stylized representation of the Braak staging for Parkinson's disease showing the initiation sites in the medulla oblongata and olfactory bulb through to the later infiltration of Lewy pathology into the cortical regions.

**Halliday G. et al. (2011) Mov Disord 26:1015-1021**

# Evidence for G.I. -Disturbances in PD



*Regular papers*

## Parkinson's disease: the presence of Lewy bodies in Auerbach's and Meissner's plexuses

**K. Wakabayashi, H. Takahashi, S. Takeda, E. Ohama, and F. Ikuta**

Department of Pathology, Brain Research Institute, Niigata University, 1 Asahimachi, Niigata 951, Japan

**Table 1.** Occurrence of Lewy bodies (LBs) in the enteric nervous system of the alimentary tract in Parkinson's disease

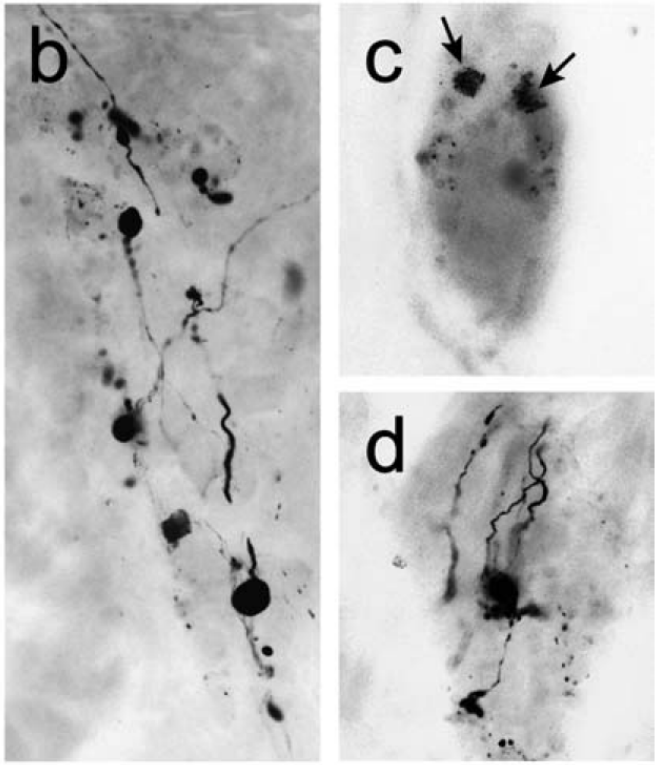
| Case no. | Age, sex (duration in years) | Esophagus | | | Sto. | Small intestine | | | Colon | | | Rec. |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Upper | Middle | Lower | | duo. | jej. | ile. | asc. | trans. | des. | |
| 1 | 56, M (18) | | | ●● ●● ●●● | | | ○ | | | | ○○ | |
| 2 | 56, F (<1) | | | ● | ● | | | | | | | ○ |
| 3 | 59, M (16) | ● | ● | ●● ●● ●●● | | | | | | | | |
| 4 | 61, M (7) | N.E. | | N.E. | | N.E. | | | ○ | N.E. | N.E. | N.E. |
| 5 | 65, M (8) | | ●●● ●●● ●●● | ●●●● ●●●● ●●●●★ ●●●●★ | ● | | | | | | | |
| 6 | 65, M (3) | | ● | ●● ●● | | ●● ●● | | | | | | |
| 7 | 75, F (27) | | | ●● | | | ●● | | ● | | | ●● |

Acta Neuropathol 1988; 76:217-221

- Occurence of Lewy-Bodies in Auerbach and Meissner Plexus
- Predilection of LB in the upper GI-tract

# α-Synuclein Inclusions in the ENS






Gastric α-synuclein immunoreactive inclusions in Meissner's and Auerbach's plexuses in cases staged for Parkinson's disease-related brain pathology

Heiko Braak [a,*], Rob A.I. de Vos [b], Jürgen Bohl [c], Kelly Del Tredici [a]

[a] *Institute for Clinical Neuroanatomy, J.W. Goethe University Clinic, Theodor Stern Kai 7, 60590 Frankfurt/Main, Germany*
[b] *Laboratorium Pathologie Oost Nederland, Burg Edo Bergmalaan 1, AD 7512 Enschede, The Netherlands*
[c] *Department of Neuropathology, Johannes Gutenberg University, Langenbeckstrasse 1, Mainz, Germany*

Received 25 August 2005; received in revised form 23 October 2005; accepted 4 November 2005

Neuroscience Letters 396 (2006) 67–72

- Presence of gastric α-synuclein inclusions could provide first link in susceptible neurons that extend from the enteric to the central nervous system individuals.

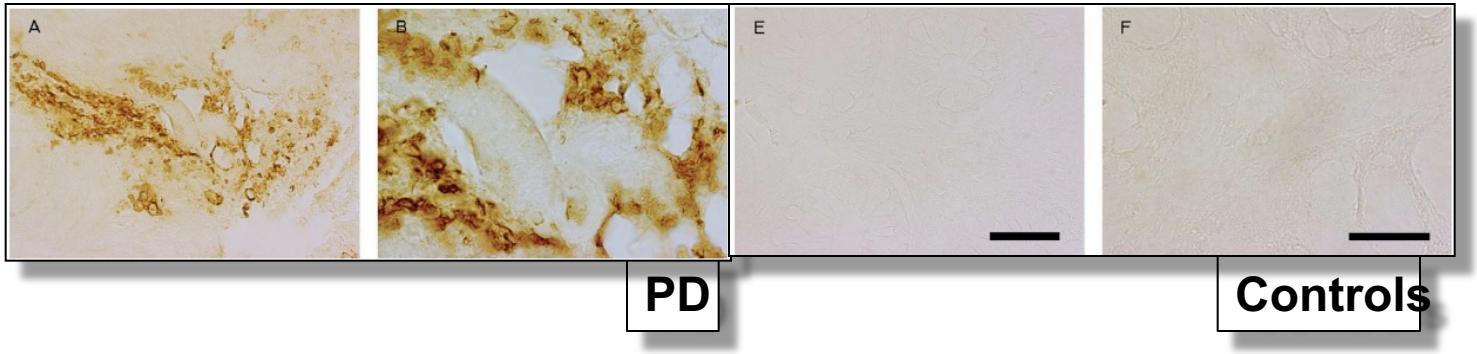
# Colon biopsies in PD



RESEARCH ARTICLE

## Alpha-Synuclein in Colonic Submucosa in Early Untreated Parkinson's Disease

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Ece Mutlu, MD,[2] Hemraj B. Dodiya, MS,[3] Delia Daian,[2] Jean A. Jaglin, RN,[1] and Jeffrey H. Kordower, PhD[3]




- 10 untreated Parkinson patients ; all positive for Alpha-Synuclein
- Sigmoidoscopy and Bx: alpha-Synuclein and 3-Nitro-Tyrosin (marker for mitochondrial stress)

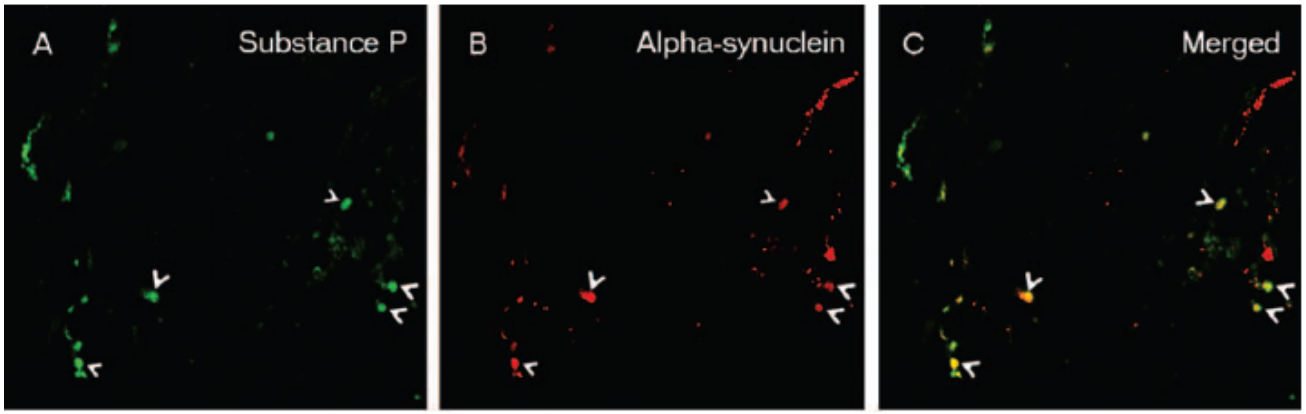
Mov Disord 2012: 27:709-715

# Premotor PD and Colon biopsy



## Is Alpha-Synuclein in the Colon a Biomarker for Premotor Parkinson's Disease? Evidence from 3 Cases

Kathleen M. Shannon, MD,[1]* Ali Keshavarzian, MD,[2] Hemraj B. Dodiya, MS,[3] Shriram Jakate, MD,[4] and Jeffrey H. Kordower, PhD[3]




- Alpha-Synuclein positive immunohistochemistry in 3 biopsies 2-5 yrs before onset

Mov Disord 2012: 27:716-719

# Why do we have conflicting results for a-Syn pathlogy in the gut?



**TABLE 2.** Issues hindering consensus on the optimal method for reliable and reproducible GI ASN detection

| Source of heterogeneity | Suggested consensus approach |
|---|---|
| ASN-reactive antibody | • Use at least 2 antibodies reactive for different epitopes and/or variants of ASN (eg, P-ASN and T-ASN), on the same number of consecutive sections.<br>• Consider antibodies reactive for oligomeric ASN. |
| Biopsy site | • For use as clinical biomarker, prioritize low discomfort for patient (ie, flexible sigmoidoscopy) and reproducibility.<br>• For research into pathogenic mechanisms, prioritize vagal innervation (ie, esophagus and stomach). |
| Amount of stained tissue | • Apply software-based image analysis (SBIA) to adjust for variability in stained area between different biopsy samples. |
| Definition of pathological staining | • Increase sharing of images.<br>• Apply reproducible SBIA algorithms.<br>• Be aware of nonneuronal ASN staining patterns. |
| Neuronal marker | • Always use at least 1 reliable marker of nervous tissue.<br>• Selection should take into account characteristics of available tissue (superficial versus whole wall). |

Ruffmann C & Parkkinen L (2016) Movement Disord 31:193-202

# The Dresden Parkinson Model

Universitätsklinikum Carl Gustav Carus
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OPEN ACCESS Freely available online

PLoS one

# Progression of Parkinson's Disease Pathology Is Reproduced by Intragastric Administration of Rotenone in Mice

**Francisco Pan-Montojo[1,2,6]*, Oleg Anichtchik[3], Yanina Dening[1], Lilla Knels[1], Stefan Pursche[4], Roland Jung[5], Sandra Jackson[2], Gabriele Gille[2], Maria Grazia Spillantini[3], Heinz Reichmann[2], Richard H. W. Funk[1]***

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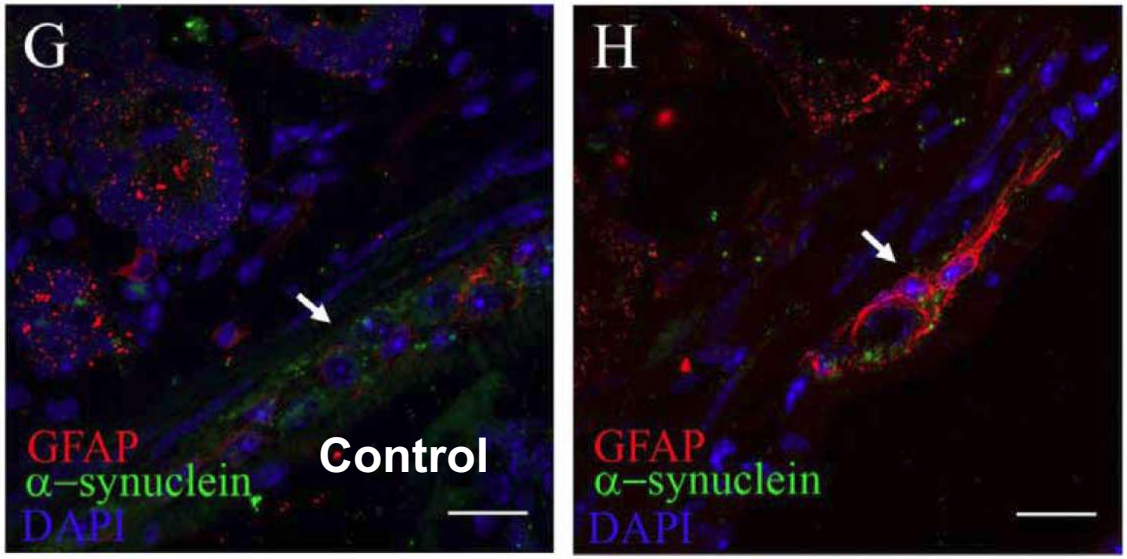
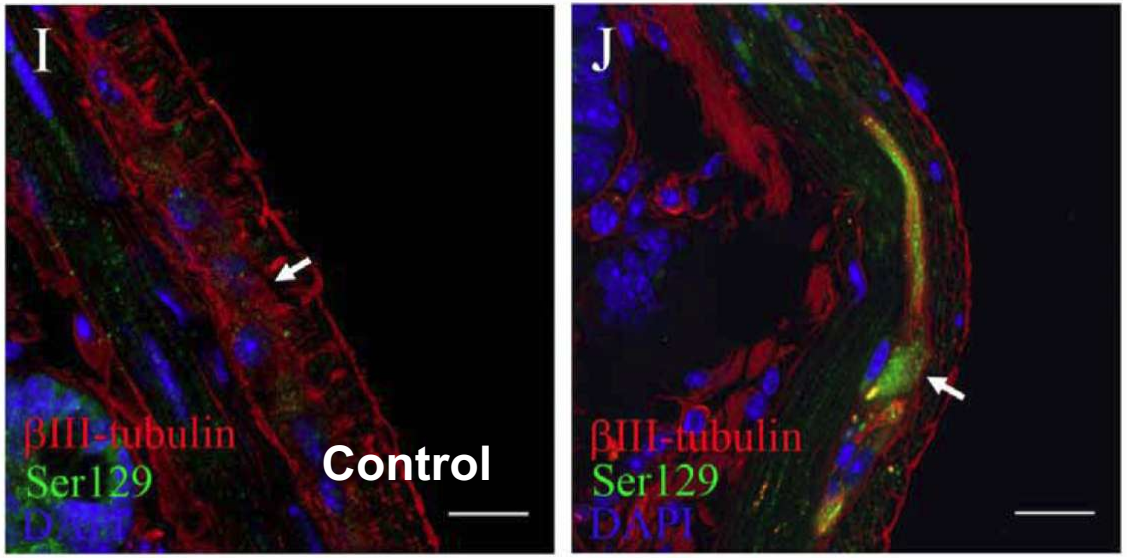


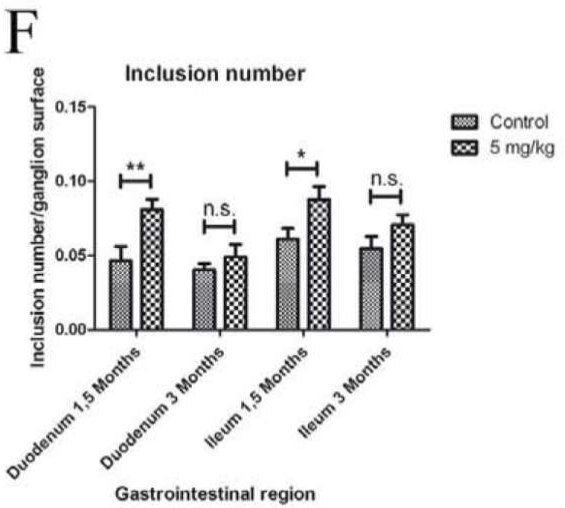






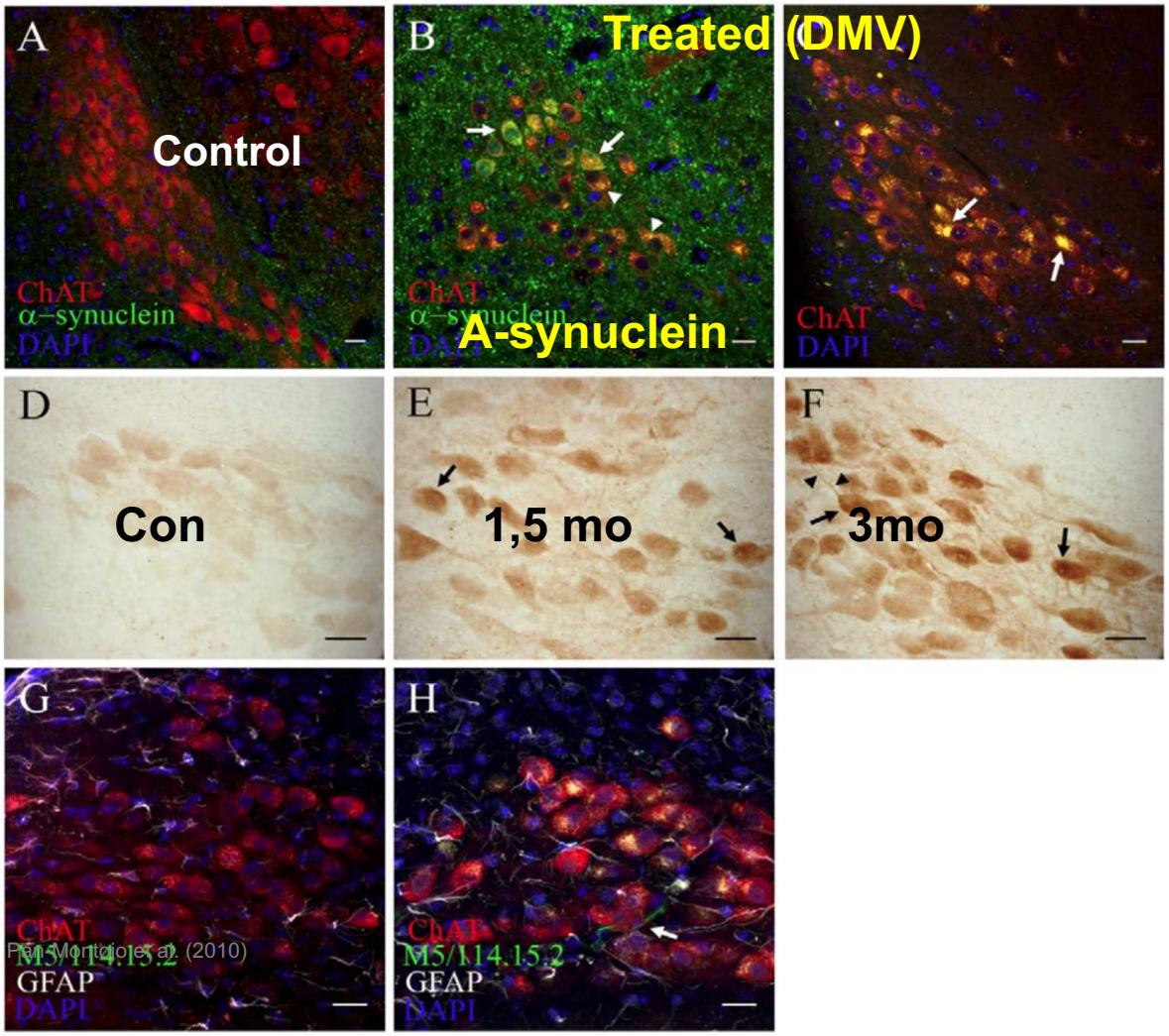







Pan-Montojo et al. (2010)

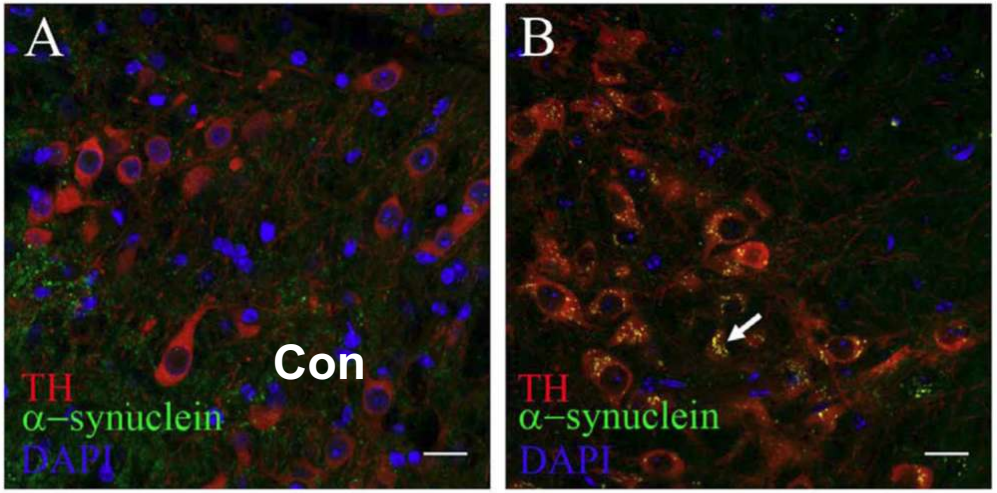
**Figure 1 (continued). Locally administered rotenone induces alpha-synuclein phosphorylation, accumulation and aggregation with gliosis in ENS ganglia.** (scale bars 20 um). **F**, each column represents total number of alpha-synuclein inclusions/ganglion surface. All graphs show mean +/- s.e.m. **G**, **H**, max-projection of staining against GFAP, alpha-synuclein and DAPI on duodenum sections from control (**G**) and treated (**H**) mice. **I**, **J**, max-projection of anti-ßIII-tubulin, antiphospho-alpha-synuclein (Ser 129) and DAPI staining on duodenum sections from control (**I**) and treated (**J**) animals.



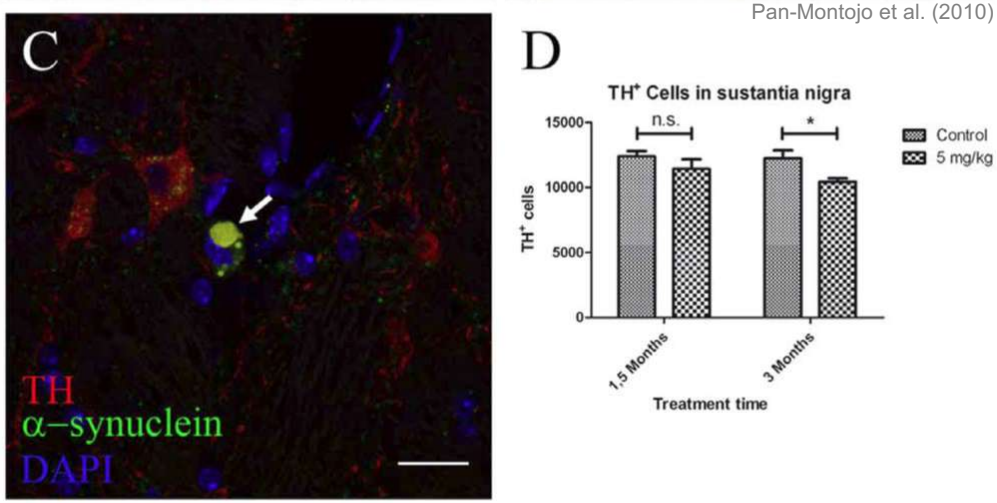

Pan-Montojo et al. (2010)

**Figure 3. Intragastrically administered rotenone induces alpha-synuclein accumulation, oxidative stress and inflammation in the dorsal motor nucleus vagus.** (scale bars 20 um). **A**, **B**, double-immunofluorescence staining against alpha-synuclein and ChAT on DMV sections from 1.5 months control (**A**) and 1.5 months treated (**B**) mice. Arrows in **B**, increased intracellular alpha-synuclein in DMV neurons already after 1.5 months. Arrowheads in **B**, autofluorescent punctate inclusion pattern inside ChAT+ neurons. **C**, DMV sections stained with ChAT and DAPI were sequentially excited with 488 and 561 laser wavelengths. Arrows in **C**, large intracellular auto-fluorescent inclusions inside ChAT+ neurons of the DMV (arrows). **D**, **E**, **F**, Light microscopy images of alpha-synuclein staining from 1.5 months control (**D**), 1.5 months (**E**) and 3 months (F) treated mice. Arrows in **E** and **F**, increased staining intensity inside DMV neuronal soma in treated mice. Arrowheads in F, increased alpha-synuclein staining inside neuronal processes **G**, **H**, average-projection of triple-immunofluorescence staining against ChAT, GFAP, MHC II (clone M5/114.15.2) and DAPI on sections from control (**G**) and treated (**H**) mice after 3 month treatment. Arrow in **H**, activated microglial cell in the DMV.

# Substantia nigra pars compacta




Pan-Montojo et al. (2010)



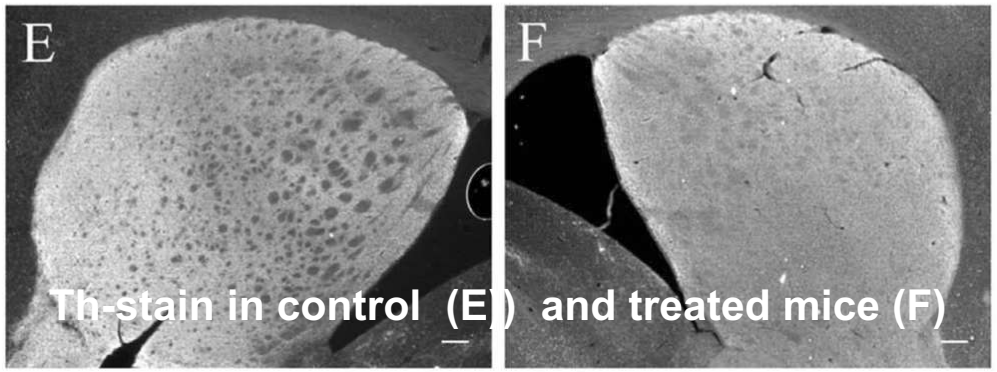




**Figure 4. Alpha-synuclein accumulation and neuronal loss in the SNc after 3 but not 1.5 months intragastrical rotenone treatment**. (**A–C**, scale bars 20 um; **E–F**, scale bars 200 um). **A, B, C**, immunostaining against TH, alpha-synuclein and DAPI on SNc sections from 1.5 months control (**A**) and 3 months (**B–C**) treated mice. Arrow in **B**, alpha-synuclein small inclusions inside TH+ neurons. Arrow in **C**, large alpha-synuclein inclusion (|>8.14 um) inside a dopamineric neuron in the SN. **D**, stereological quantification (n = 3) of TH+ neurons in the SN from control and treated mice. Asterisk, P<0.05. Number of neurons was determined based on the optical fractionator principle using StereoInvestigator software (MicroBrightField Inc., Williston, USA). Each column represents total number of TH+ neurons in the SN in 1.5 and 3 months control and treated mice. Graph shows mean +/-s.e.m. **E, F**, TH immunostaining on striatum in 1.5 months control (**E**) and 3 months treated (**F**) mice.

# The vagus nerve



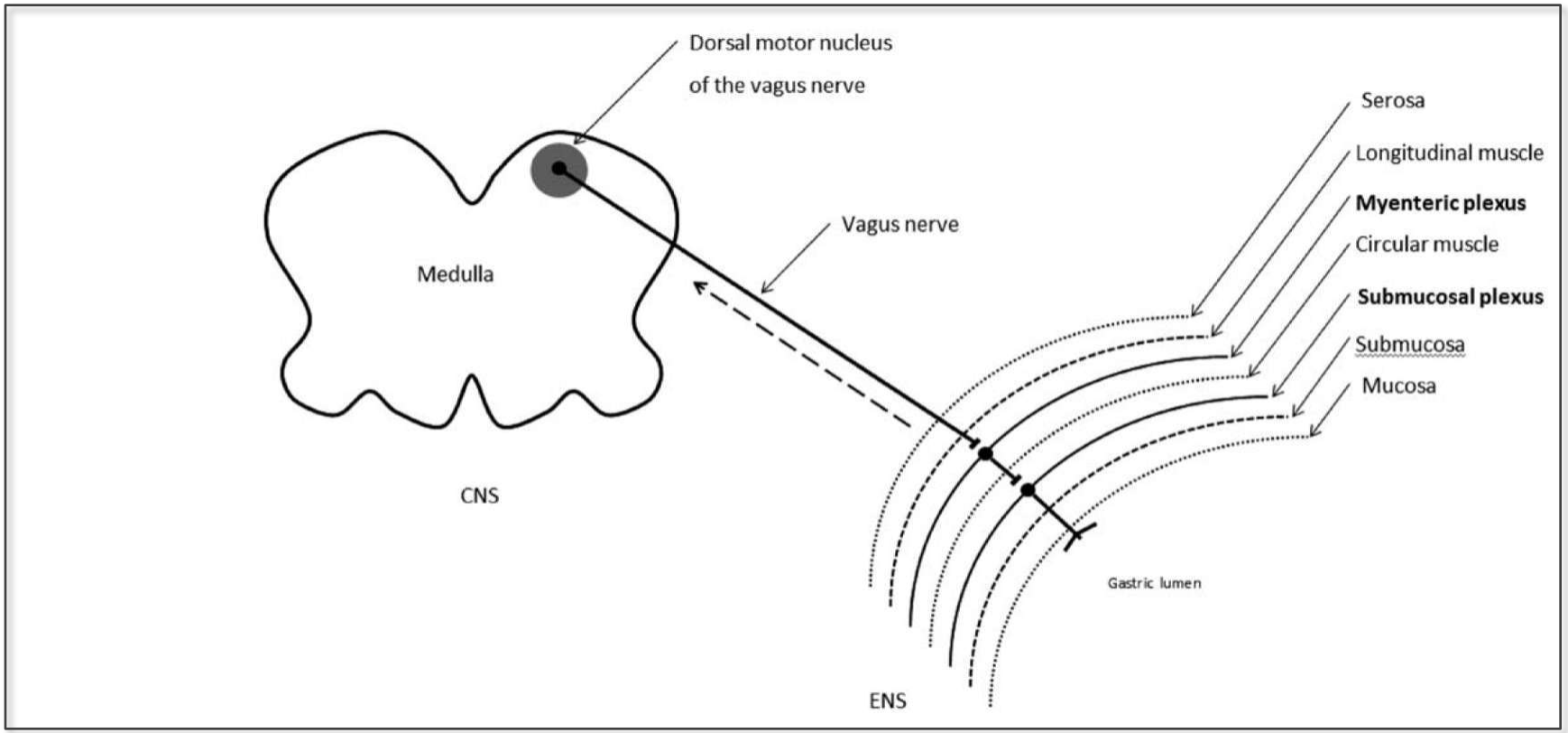



**FIG. 1.** Interaction of the central nervous system with the enteric nervous system via the vagus nerve

Marrinan S et al. (2014) Movement Disorders 26:23-32

# Further Evidence



## Hemivagotomy and partial sympathectomy delay Parkinson's disease progression in mice

Francisco Pan-Montojo[1,2,5], Mathias Schwarz[1], Clemens Winkler[1], Mike Arnhold[2], Gregory O'Sullivan[4], Arun Pal[4], Margarita Rodrigo-Angulo[5], Gabriele Gille[2], Richard H.W. Funk[1,3,] and Heinz Reichmann[2,3]

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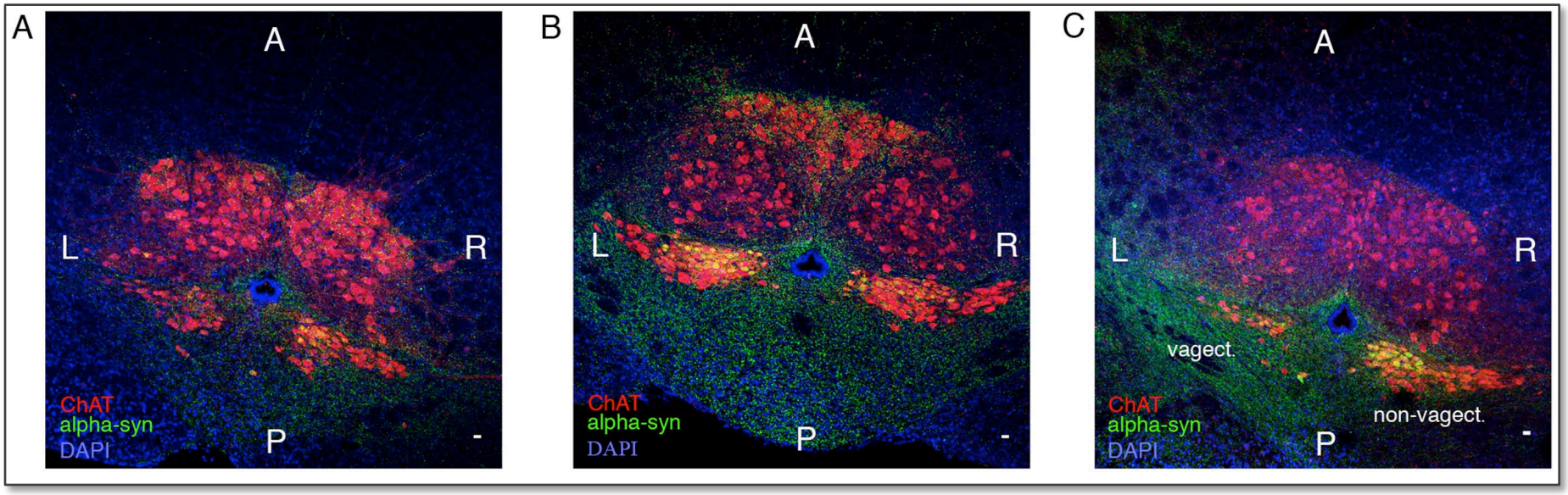
*[2]Department of Neurology, University Hospital Carl-Gustav Carus, Fetscherstr. 74, 01307, Dresden, Germany*
*[3]Center for Regenerative Therapies Dresden, Tatzberg 47/49, 01307, Dresden, Germany*
*[4]Max-Planck Institute for Cell Biology and Genetics, Pfotenhauerstr. 108, 01307, Dresden, Germany*
*[5]Departamento de Anatomía, Histología y Neurociencia, Facultad de Medicina, Universidad Autónoma de Madrid, Arzobispo Morcillo 4, 28029 Madrid, Spain*

### Abstract

Pathological studies on Parkinson's disease (PD) patients suggest that PD pathology starts at the olfactory bulb (OB) and the enteric nervous system (ENS) progressing into the central nervous system (CNS). In our previous study, we showed that the local effect of rotenone on the ENS reproduces this pathological progression in mice affecting only synaptically connected structures, suggesting transsynaptic and retrograde axonal transport as underlying mechanisms of this progression. Here, we tested this hypothesis by performing a hemivagotomy or a partial sympathectomy prior to rotenone oral treatment on mice and using primary enteric and sympathetic neuron co-cultures. For the first time, our results show that the appearance of motor dysfunctions is delayed in hemi-vagotomized and sympathectomized treated mice when compared to non-operated treated mice. Moreover, we only observed accumulation of alpha-synuclein in those structures still connected to the ENS. Interestingly, enteric neurons secrete alpha-synuclein only upon exposure to rotenone and secreted alpha-synuclein can be up-taken by non-neuronal cells or presynaptic sympathetic neurons. Altogether, these results suggest that pesticide-dependent alterations in the ENS can induce idiopathic PD pathology and trigger its progression. Moreover, it seems that this progression is based on the transsynaptic and retrograde axonal transport of alpha-synuclein, playing here the role of a prionic protein.

**Pan-Montojo et al. (2012)**
**Science Rep 2:898 f**




**Pan-Montojo et al. (2012) Science Rep 2:898 f**

RESEARCH ARTICLE

# Vagotomy and Subsequent Risk of Parkinson's Disease

Elisabeth Svensson, PhD,[1] Erzsébet Horváth-Puhó, PhD,[1]
Reimar W. Thomsen, PhD,[1] Jens Christian Djurhuus, DMSc,[2] Lars Pedersen, PhD,[1]
Per Borghammer, DMSc,[2,3] and Henrik Toft Sørensen, DMSc[1]

**Objective:** Parkinson's disease (PD) may be caused by an enteric neurotropic pathogen entering the brain through the vagal nerve, a process that may take over 20 years. We investigated the risk of PD in patients who underwent vagotomy and hypothesized that truncal vagotomy is associated with a protective effect, whereas superselective vagotomy has a minor effect.
**Methods:** We constructed cohorts of all patients in Denmark who underwent vagotomy during 1977–1995 and a matched general population cohort by linking Danish registries. We used Cox regression to compute hazard ratios (HRs) for PD and corresponding 95% confidence intervals (CIs), adjusting for potential confounders.
**Results:** Risk of PD was decreased in patients who underwent truncal (HR = 0.85; 95% CI = 0.56–1.27; follow-up of >20 years: HR = 0.58; 95% CI: 0.28–1.20) compared to superselective vagotomy. Risk of PD was also decreased after truncal vagotomy when compared to the general population cohort (overall adjusted HR = 0.85; 95% CI: 0.63–1.14; follow-up >20 years, adjusted HR = 0.53; 95% CI: 0.28–0.99). In patients who underwent superselective vagotomy, risk of PD was similar to the general population (HR = 1.09; 95% CI: 0.84–1.43; follow-up of >20 years: HR = 1.16; 95% CI: 0.80–1.70). Statistical precision of risk estimates was limited. Results were consistent after external adjustment for unmeasured confounding by smoking.
**Interpretation:** Full truncal vagotomy is associated with a decreased risk for subsequent PD, suggesting that the vagal nerve may be critically involved in the pathogenesis of PD.

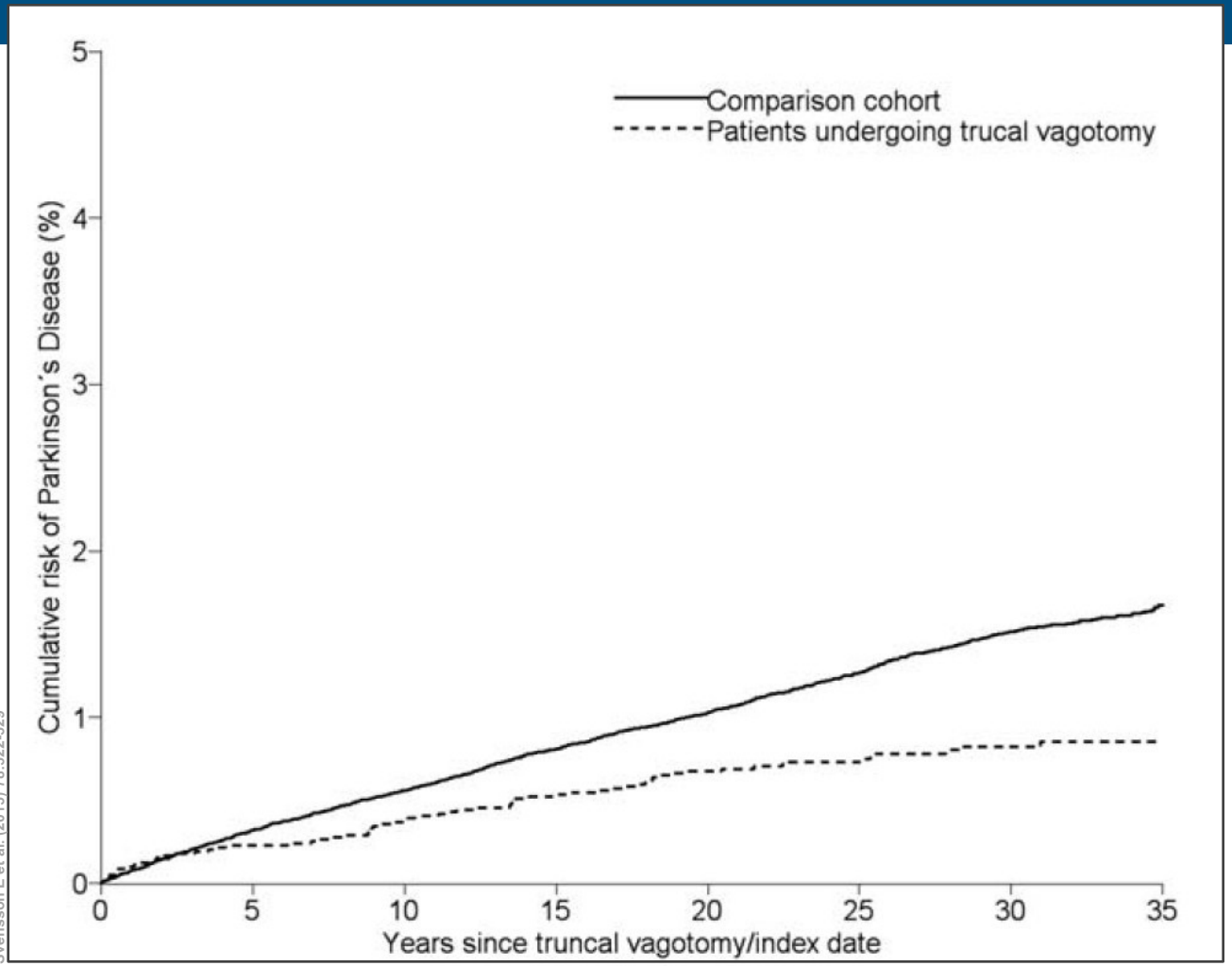
ANN NEUROL 2015;78:522–529

**TABLE 1.** Epidemiological studies investigating vagotomy and subsequent PD risk

| | | Vagotomy | | | | No vagotomy | |
|---|---|---|---|---|---|---|---|
| Author | Country | Number | Classification | Age at surgery, mean | Year of vagotomy | Number | Key findings |
| Liu et al., 2017[24] | Sweden | 9,430 | Truncal vs selective (including both selective and highly selective) | 54.3 years | 1970-2010 | 377,200 | When cases restricted to >5 years after the date of surgery, truncal (but not selective) vagotomy had lower PD risk |
| Svensson et al., 2015[26] | Denmark | 11,209[a] | Truncal (including both truncal and selective) vs highly selective[b] | 56 years (truncal), 47 years (highly selective) | 1977-1995 | 127,211 | Truncal vagotomy had statistically non-significant reduction in PD risk >5 years after surgery, but stronger effect when restricted >20 years |
| Tysnes et al., 2015[27] | Denmark | 15,079 | Truncal vs selective[b] | NR | 1977-2011 | NR[c] | No significant risk reduction found |

All studies were nationwide cohort studies with data linkage. NR, not reported.
[a]Although 14,883 vagotomy patients were identified, only 11,209 had more than 5 years of postsurgical follow-up.
[b]Different operative coding classification applied to the same data source.
[c]The number of cases without vagotomy was not reported, but this data was available to calculate relative risk reduction for the development of PD in patients undergoing different vagotomy procedures.

**Breen DP et al. (2019) Movement Disord 34:307-316**




Svensson E et al. (2015) 78:522-529

FIGURE 1: Cumulative incidence curves of Parkinson's disease for patients who underwent truncal vagotomy compared to a matched general population cohort.

# Incidence of PD Among Patients with Inflammatory Bowel disease



## Killinger et al. Sci. Trans. Med. (2018)

- In two independent studies involving more than 1.6 million individuals and over 91 million person-years, they observed that removal of the appendix decades before PD onset was associated with a lower risk for PD, and delay of disease onset.
- The healthy human appendix contained intraneuronal alpha-synuclein aggregates and an abundance of PD pathology-associated alpha-synuclein truncation products that are known to accumulate in Lewy bodies.
- They propose that the normal human appendix contains pathogenic forms of alpha-synuclein that affect the risk of developing PD.

# Incidence of PD Among Patients with Inflammatory Bowel disease



## Peter et al. JAMA Neurology (2018) 75:939-946

- To compare the incidence of PD among individuals with or without IBD and to assess whether PD risk among patients with IBD is altered by anti-TNF therapy.
- 144.018 individuals with IBD. The incidence of PD among patients with IBD was 28% higher than that among unaffected matched controls.
- A 78% reduction in the incidence rate of PD was detected among patients with IBD who were exposed to anti-TNF therapy.

Mov Disord. 2018 Sep;33(9):1492-1496

BRIEF REPORTS

# Appendectomy and Risk of Parkinson's Disease in Two Large Prospective Cohorts of Men and Women

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who did not was 1.08 (95% confidence interval, 0.94-1.23). In women, appendectomy for appendicitis, but not incidental appendectomy, was associated with a modestly elevated risk of Parkinson's disease (hazard ratio, 1.23 [95% confidence interval, 1.00-1.50]).
**Conclusions:** Overall, this study suggests limited to no association between appendectomy and Parkinson's disease risk. © 2018 International Parkinson and Movement Disorder Society

**Key Words:** appendectomy; Parkinson's; epidemiology; gut-brain axis

Parkinson's disease (PD) is increasingly recognized as a systemic disease, with well-known effects on the peripheral nervous system, particularly the gut. Recently, it has been proposed that the initial misfolding of α-synuclein, a protein key to PD pathology, may occur in the gut and then spread to the brain via retrograde axonal transport.[1–4] A reduced risk of PD was observed after truncal vagotomy in the Danish[5] and, to



tomy and PD has produced mixed results. In this study we examined whether history of self-reported appendectomy was related to risk of incident Parkinson's disease in the Nurses' Health Study and the Health Professionals Follow-up Study.
**Methods:** We used the Cox proportional hazards model to estimate the hazard ratio of Parkinson's disease associated with self-report of appendectomy in men and women. Among women, we estimated the hazard ratio of Parkinson's disease associated with appendectomy for appendicitis and incidental appendectomy.
**Results:** In pooled analyses, self-report of any appendectomy was not related to Parkinson's disease risk: the hazard ratio of Parkinson's disease comparing participants who reported any appendectomy with those

microbiome.

In a recent report,[17] the appendix was found to be particularly rich in α-synuclein relative to other areas of the gastrointestinal system, suggesting this organ as a potential point of initiation of PD pathology. Several studies to date have examined the association between appendectomy and PD with mixed results. In an analysis of the Danish National Registry, with 34 years of follow-up, appendectomy was associated with a modest 15% increase (95% CI, 3%-27%) in PD risk.[18] In contrast, no association between appendectomy and PD risk was found in a registry-based study in Ontario, Canada, comparing 42,999 participants with appendectomy with those with cholecystectomy or no procedures.[19]

In this study, we sought to examine the association between self-reported appendectomy and incidence of PD in 2 large prospective cohort studies, the Nurses' Health Study and the Health Professionals Follow-up Study.

## Methods

### Study Population

We investigated the association between self-reported appendectomy and risk of PD in 2 large prospective epidemiological cohorts: the Nurses' Health Study (NHS) and the Health Professionals Follow-up Study

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**Published online 00 Month 2018 in Wiley Online Library (wileyonlinelibrary.com). DOI: 10.1002/mds.109**

# Appendectomy does not cause lower PD risk



**TABLE 1.** Any appendectomy and risk of Parkinson's disease in women (NHS) and men (HPFS)

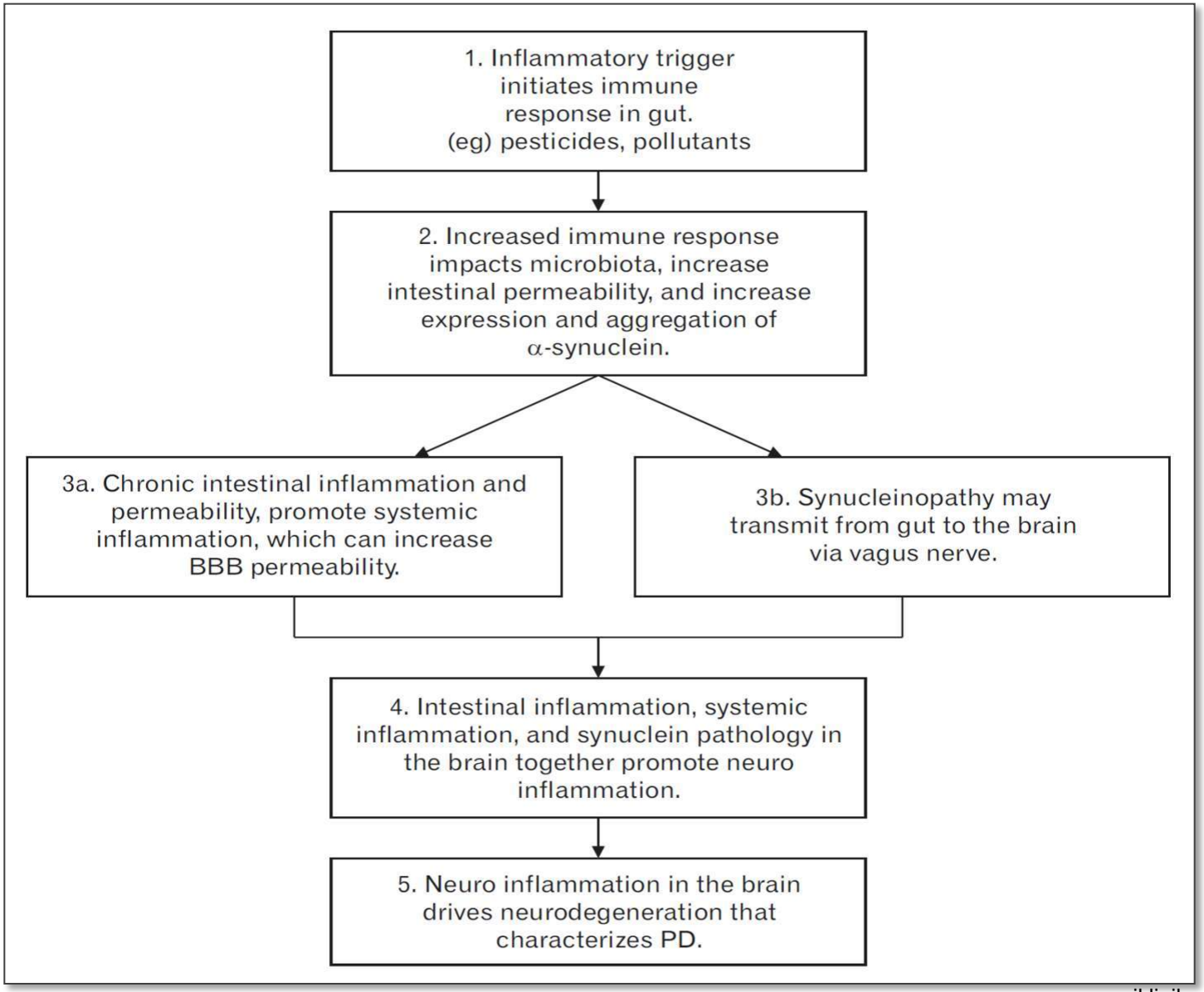
| | | Women | | | | Men | | | | Pooled | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | PY[1] | Cases | HR | 95% CI | PY | Cases | HR | 95% CI | HR | 95% CI | p-Heterogeneity (sex) |
| No appendectomy | | 1,249,191 | 406 | Ref | | 842,764 | 460 | Ref | | | | |
| Any appendectomy | Model 1 | 442,700 | 177 | 1.09 | (0.92-1.31) | 167,509 | 109 | 1.02 | (0.83-1.26) | 1.06 | (0.93-1.22) | 0.62 |
| | Model 2 | | | 1.08 | (0.91-1.30) | | | 1.04 | (0.84-1.29) | 1.08 | (0.94-1.23) | 0.72 |

Model 1 adjusted for age in months at baseline.
Model 2 adjusted for age in months, smoking (never, past, current), pack-years smoking, PMH use (in NHS only: never, past, current) at baseline.
[1] Person-years of follow-up

**Palacios N et al. (2018) Movement Disord 33(9):1492-1496.**

# Interplay of gut-brain axis

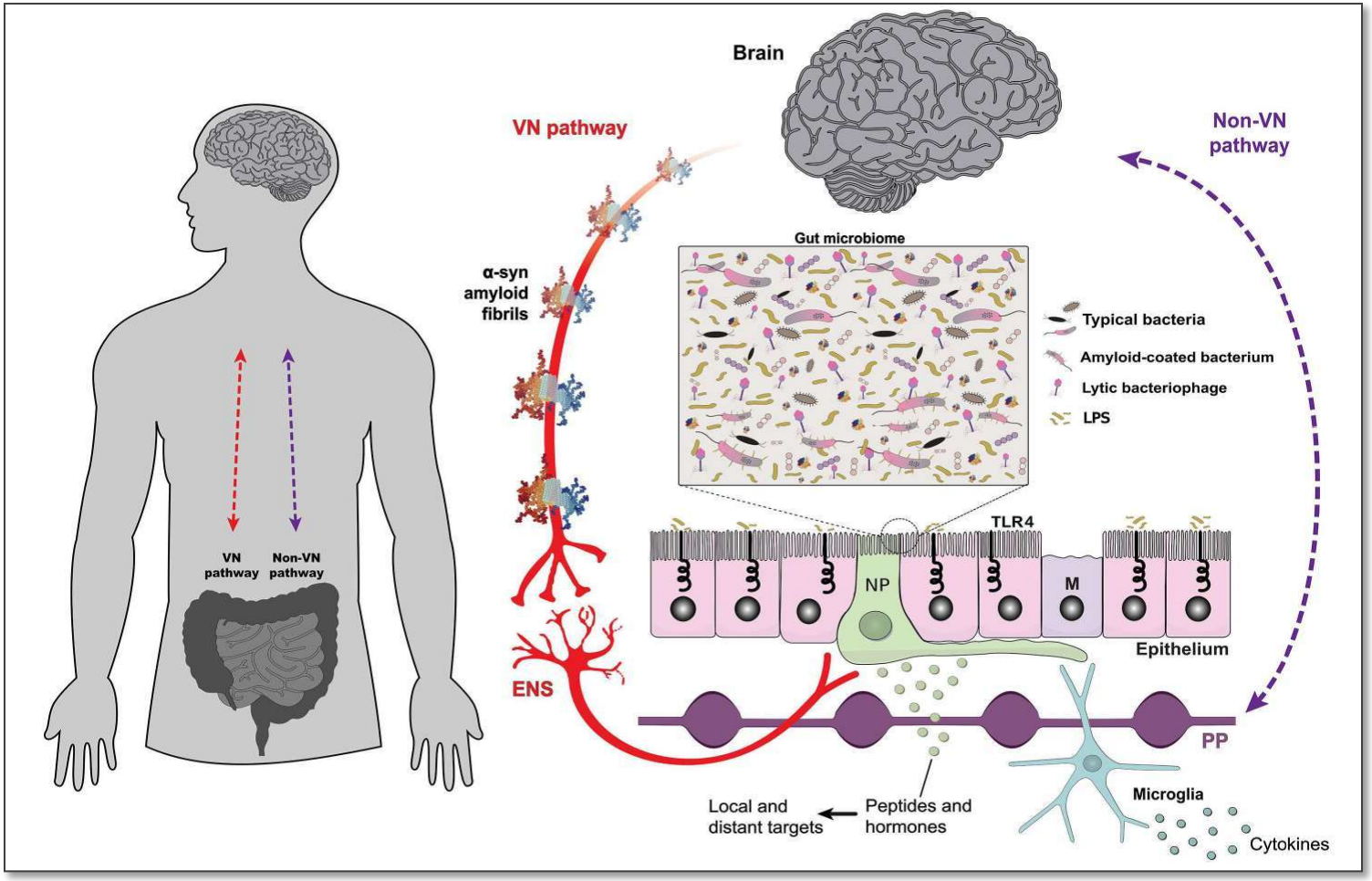





Nair AT et al. (2018) J Neurogastroenterol Motil 24:30-42

# The gut and PD- A bidirectional pathway






Fonesca Santos S et al. (2019) Front Neurol: 10.3389/fneur.2019.00574

# The gut-brain axis in health and disease



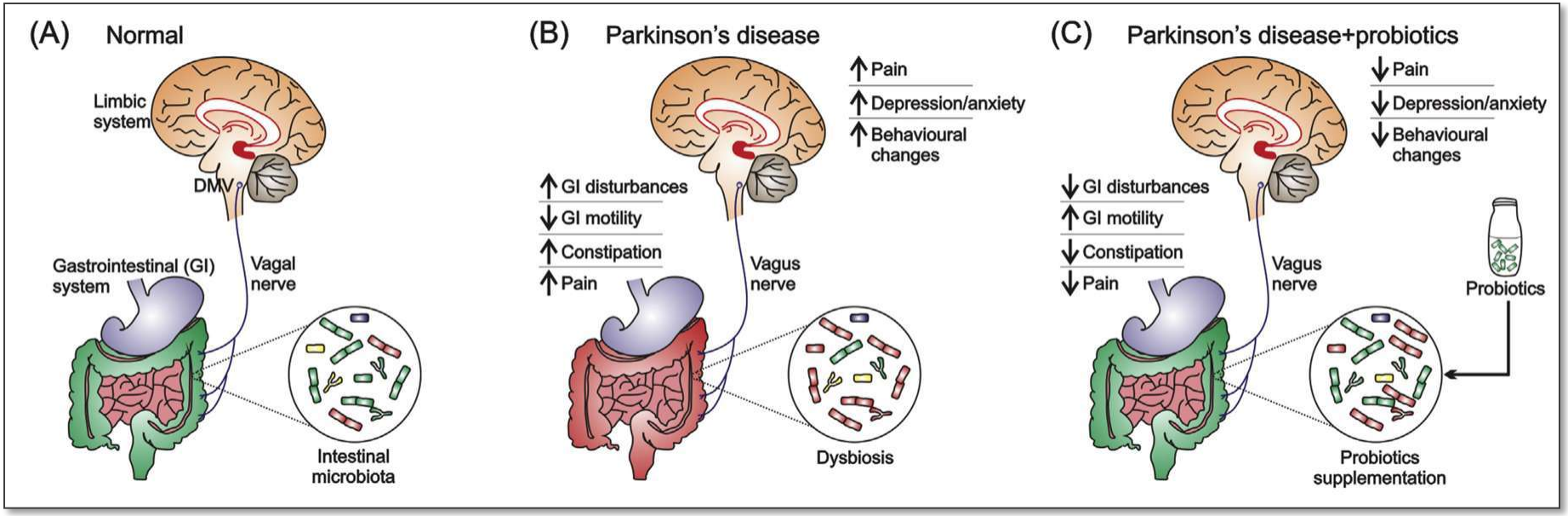



**Fig. 1.** The brain-gut axis in health and disease, with relevance to Parkinson's disease. (A) The healthy bi-directional communication between the brain and the gut, high-lighting the involvement of the vagus nerve. (B) The brain-gut axis and non-motor symptoms of Parkinson's disease including both central and GI dysfunction. (C) The manipulation of the gut microbiota through the use of probiotics and potential alleviation of non-motor symptoms of Parkinson's disease. SN: substantia nigra; DMV: dorsal motor nucleus of the vagus.

**Felice VD et al. (2016) Parkinsonism Rel Disord 27:1-8**

# On the function of Probiotics in PD



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DOI 10.1007/s12275-018-8032-4
eISSN 1976-3794
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REVIEW

## Mind-altering with the gut: Modulation of the gut-brain axis with probiotics

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**It is increasingly evident that bidirectional interactions exist among the gastrointestinal tract, the enteric nervous system, and the central nervous system. Recent preclinical and clinical trials have shown that gut microbiota plays an important role in these gut-brain interactions. Furthermore, alterations in gut microbiota composition may be associated with pathogenesis of various neurological disorders, including stress, autism, depression, Parkinson's disease, and Alzheimer's disease. Therefore, the concepts of the microbiota-gut-brain axis is emerging. Here, we review the role of gut microbiota in bidirectional interactions between the gut and the brain, including neural, immune-mediated, and metabolic mechanisms. We highlight recent advances in the understanding of probiotic modulation of neurological and neuropsychiatric disorders via the gut-brain axis.**

***Keywords***: probiotics, gut microbiota, nervous system, gut-brain axis, gut dysbiosis, neurological disorders

*al.*, 2011). The scaffolding of the gut-brain axis includes the gastrointestinal tract, central nervous system (CNS), autonomic nervous system (ANS), enteric nervous system (ENS), neuroendocrine system, and immune system (Grenham *et al.*, 2011). Recent studies have shown that the gut microbiota is involved in the neurodevelopment and diverse brain functions through regulating the gut-brain axis (Carabotti *et al.*, 2015; Erny *et al.*, 2015). Gastrointestinal symptoms, such as constipation, diarrhea, and abdominal pain, are common comorbidities in many neurological diseases (Westfall *et al.*, 2017). Moreover, recent advances in metagenomic sequencing have revealed that dysregulation in the composition of gut microbiota (gut dysbiosis) is present in a variety of neurological diseases. Consequently, the importance of maintaining a healthy microbiota community (gut symbiosis) in the regulation of the gut-brain axis cannot be overly emphasized. The term microbiota-gut-brain (MGB) axis was introduced to highlight the role of the microbiota in the gut-brain axis.

Probiotics are defined as living microorganisms that, when ingested in adequate quantities, confer a health benefit on the host; these microorganisms have been reported to exert a wide range of effects (Hill *et al.*, 2014). Although their mechanisms in modulating host physiology are not yet fully elucidated, probiotics might be able to modulate host immune system (Bermudez-Brito *et al.*, 2012). For example, *Weissella cibaria* WIKIM28 isolated from kimchi ameliorates atopic

**Table 1. List of neuroactive compounds detected within various bacteria**

| Gut microbiota | Neurochemical | References |
|---|---|---|
| *Lactobacillus*, *Bifidobacterium* spp. | GABA | Barrett *et al.* (2012) |
| *Bifidobacterium infantis*, *Streptococcus*, *Escherichia*, *Enterococcus*, *Lactococcus*, *Lactobacillus*, *Candida*, | Serotonin (5-HT) | Özogul (2011), Holzer and Farzi (2014) |
| *Clostridium sporogenes*, *Ruminococcus gnavus* | Tryptamine | Williams *et al.* (2014) |
| *Escherichia*, *Bacillus*, *Saccharomyces* | Norepinephrine | Holzer and Farzi (2014) |
| *Escherichia*, *Bacillus*, *Lactococcus*, *Lactobacillus*, *Serratia* | Dopamine | Özogul (2011), Holzer and Farzi (2014) |
| *Lactobacillus*, *Bacillus* | Acetylcholine | Kawashima *et al.* (2007) |
| *Lactococcus*, *Lactobacillus*, *Streptococcus*, *Enterococcus* | Histamine | Landete *et al.* (2008), Thomas *et al.* (2012), Hemarajata *et al.* (2013) |
| *Bacillus* sp. JPJ | L-dopa | Surwase and Jadhav (2011) |

**Kim Net al. (2018) J Microbiol 56(3):172-182**

**Table 2. Links between altered gut microbiota composition and a variety of neurological and psychiatric disorders**

| Disease | Altered gut microbiota | References |
|---|---|---|
| Stress | Porphyromonadaceae ↓ | Bailey *et al.* (2010) |
| | *Clostridium* ↑, *Bacteroides* ↓ | Bailey *et al.* (2011) |
| | *Oscillibacter* ↑, *Anaerotruncus* ↑, *Peptococcus* ↑, *Lactobacillus* ↓ | Golubeva *et al.* (2015) |
| Depression | *Bifidobacterium* ↓, *Lactobacillus* ↓ | Aizawa *et al.* (2016) |
| | Bacteroidetes ↑, Proteobacteria ↑, Actinobacteria ↑, Firmicutes ↓ | Jiang *et al.* (2015) |
| Autism | *Clostridium* ↑ | Song *et al.* (2004), Parracho *et al.* (2005) |
| | *Sutterella* spp. ↑, *Ruminococcus torques* ↑, *Akkermansia muciniphila* ↓ | Wang *et al.* (2011, 2013) |
| | *Clostridium* ↑, Sutterellaceae ↑, Enterobacteriaceae ↑, *Bifidobacterium* ↓ | De Angelis *et al.* (2013) |
| | *Collinsella* ↑, *Corynebacterium* ↑, *Dorea* ↑, *Lactobacillus* ↑, *Alistipes* ↓, *Bilophila* ↓, *Dialister* ↓, *Parabacteroides* ↓, *Veillonella* ↓ | Strati *et al.* (2017) |
| | *Desulfovibrio* ↑, *Bacteroides vulgatus* ↑, *Ruminococcus* ↑, *Bifidobacterium* ↓ | Finegold *et al.* (2010) |
| Alzheimer's disease | Association with bacterial and viral infection | Bu *et al.* (2015) |
| | Bacteroidetes ↑, Tenericutes ↑, Firmicutes ↓, Verrucomicrobia ↓, Proteobacteria ↓ Actinobacteria ↓, *Allobaculum* ↓, *Akkermansia* ↓ | Harach *et al.* (2017) |
| | Bacteroidetes ↑, Firmicutes ↓, *Bifidobacterium* ↓ | Vogt *et al.* (2017) |
| Parkinson's disease | *Ralstonia* ↑, *Blautia* ↓, *Coprococcus* ↓, *Roseburia* ↓, *Faecalibacterium* ↓ | Keshavarzian *et al.* (2015) |
| | Enterobacteriaceae ↑, Prevotellaceae ↓ | Scheperjans *et al.* (2015) |

**Kim Net al. (2018) J Microbiol 56(3):172-182**

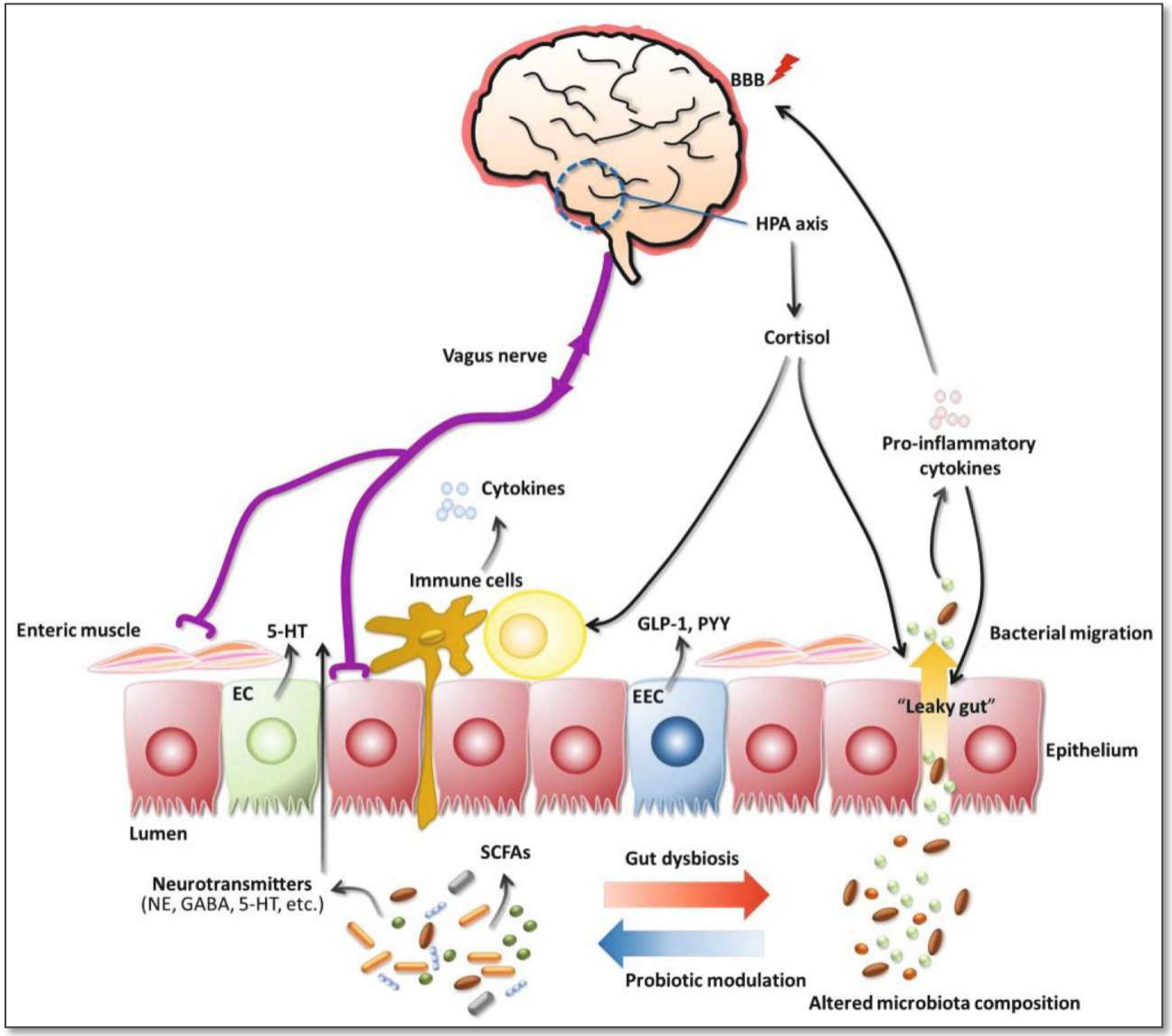


**Fig. 1. Modulation of the gut-brain axis by probiotics.** The routes of communication between the gut and the brain include neuronal, immune-mediated, and metabolite-mediated pathways. Gut dysbiosis leads to increased inflammation, as well as, activation of the HPA axis, and altered levels of neurotransmitters and bacterial metabolites; these may contribute to abnormal signaling through the vagus nerve. Reduced integrity of the gastrointestinal barrier triggers bacterial migration ("leaky gut") and inflammation. Inflammatory cytokines induce the disruption of blood-brain barrier integrity. Probiotics have the potential to normalize such processes (Abbreviations: HPA axis, hypothalamus-pituitary gland-adrenal gland axis; NE, norepinephrine; GABA, γ-aminobutyric acid; BBB, blood brain barrier; EEC, enteroendocrine cell; EC, enterochromaffin cell); GLP-1, glucagon-like peptide-1; PYY, peptide tyrosine tyrosine; 5-HT, 5-hydroxytryptamine; SCFAs, short-chain fatty acids.

Kim Net al. (2018) J Microbiol 56(3):172-182

976 *Movement* Disorders, Vol. 29, No. 8, 2014

VIEWPOINT

# Gut Feelings About Smoking and Coffee in Parkinson's Disease

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**ABSTRACT:** Strong epidemiologic evidence suggests that smokers and coffee drinkers have a lower risk of Parkinson's disease (PD). The explanation for this finding is still unknown, and the discussion has focused on two main hypotheses. The first suggests that PD patients have premorbid personality traits associated with dislike for coffee-drinking and smoking. The second posits that caffeine and nicotine are neuroprotective. We propose an alternative third hypothesis, in which both cigarette and coffee consumption change the composition of the microbiota in the gut in a way that mitigates intestinal inflammation. This, in turn, would lead to less misfolding of the protein alpha-synuclein in enteric nerves, reducing the risk of PD by minimizing propagation of the protein aggregates to the central nervous system, where they otherwise can induce neurodegeneration. © 2014 International Parkinson and Movement Disorder Society

**Key Words:** Parkinson's disease; enteric nervous system; nicrobiota

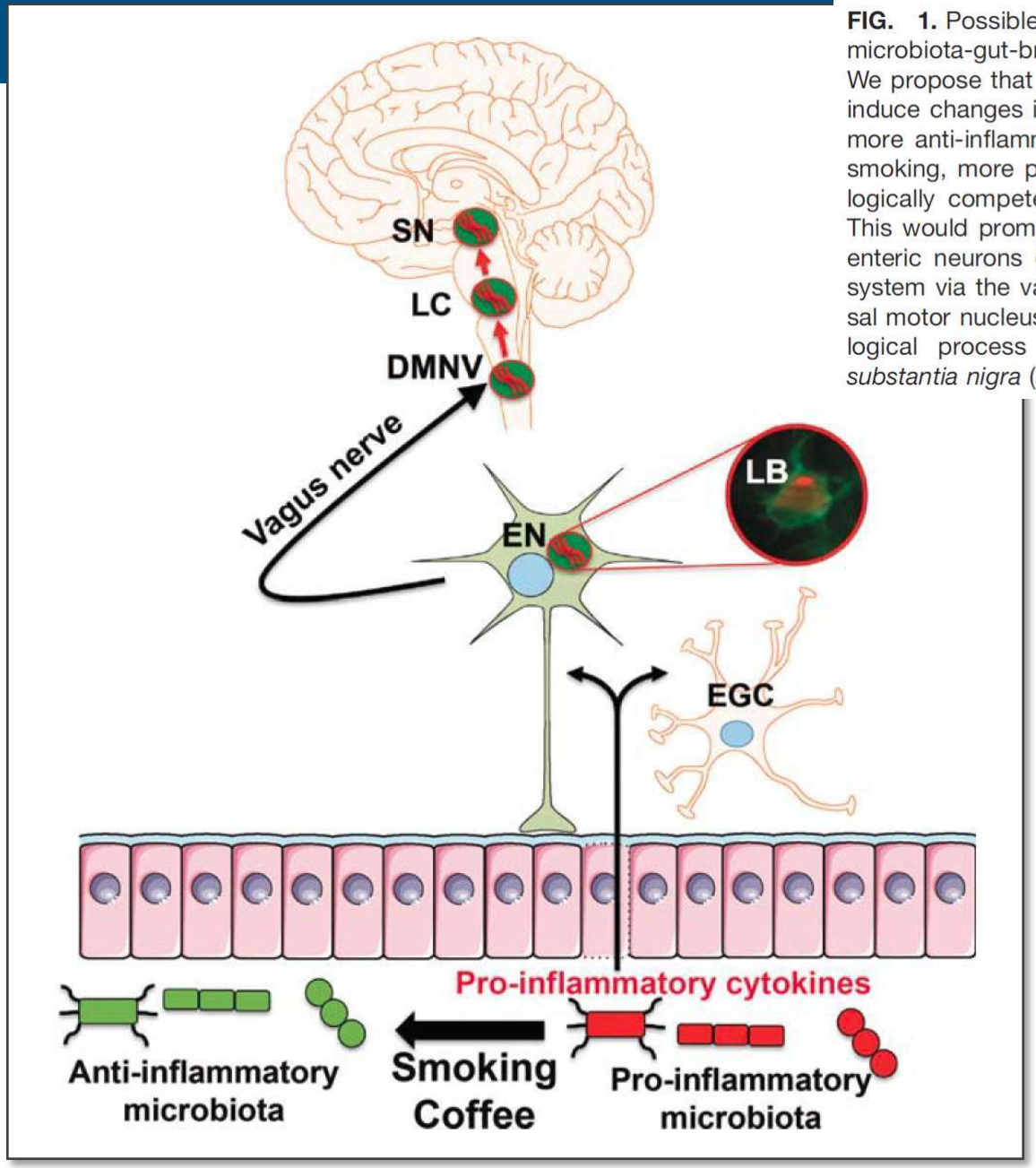
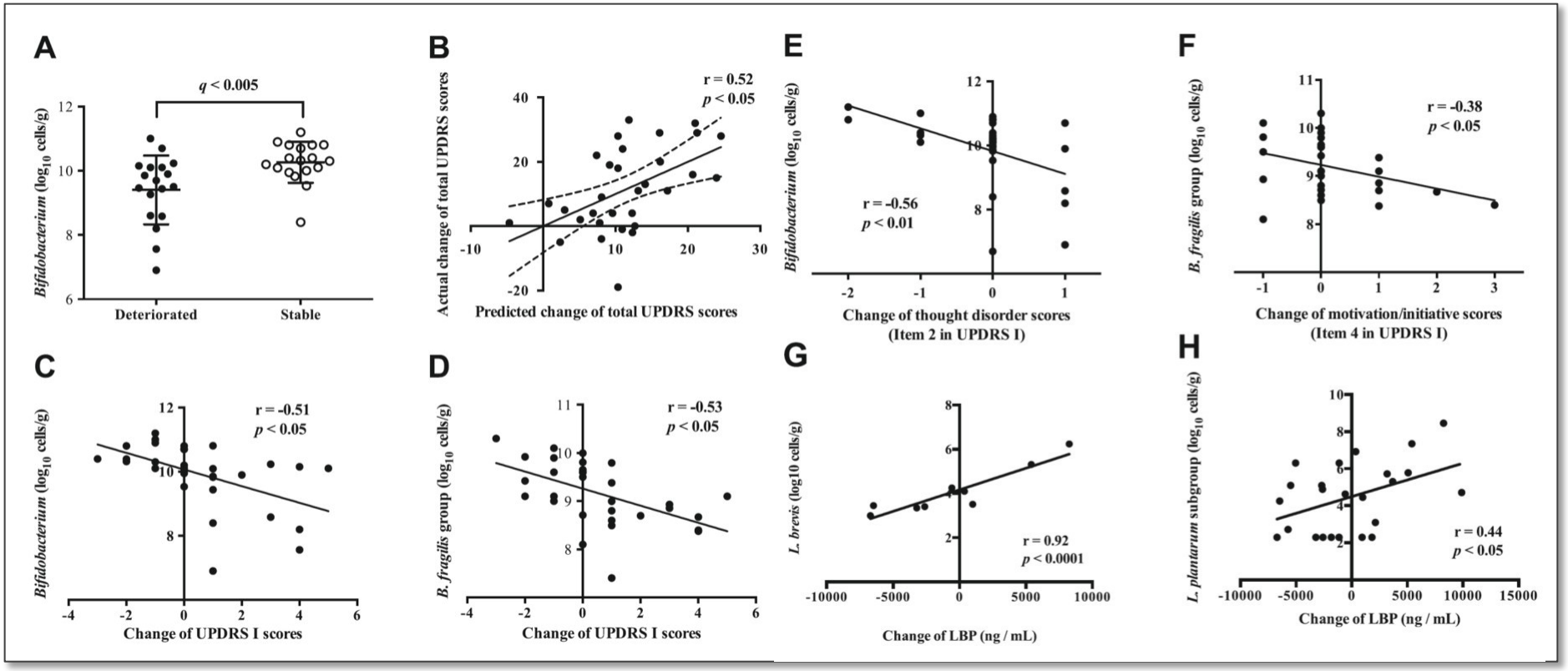



**FIG. 1.** Possible role of smoking and coffee consumption on microbiota-gut-brain-axis and the development of Parkinson's disease. We propose that both cigarette smoking and coffee consumption may induce changes in the composition of microbiota with a shift toward a more anti-inflammatory state. In the absence of coffee and cigarette smoking, more pro-inflammatory cytokines are produced by immunologically competent cells and by enteric glial cells (EGC) in the gut. This would promote a-synuclein aggregation (Lewy bodies, LB) within enteric neurons (EN) that may spread further to the central nervous system via the vagal preganglionic innervation of the gut and the dorsal motor nucleus of the vagus (DMNV). After several years, the pathological process would reach the *locus coeruleus* (LC) and the *substantia nigra* (SN).

**Derkinderen P et al. (2014) Mov Disord 29:967**

# The gut microbiota in PD






Lin et al. (2018) PRD53:82-88: Significant increases in the abundance of 4 bacterial families and decreases in seventeen bacterial families in China.

# Summary



**Parkinson‘s Disease seems to follow a clinical pattern with a pre-motor phase followed by the typical motor impairment**

**Early signs are in most patients present and consist of loss of olfaction and constipation**

**This fits well with the claim that Braak stage 1 is characterised by alpha-synuclein in the dorsal vagal nc. and the olfactory bulb.**

**More recent neuropathological work has shown that there is also impairment of the ENS and the nervous system of the submandibular gland**

**All these locations are open to the environment, thus it is intriguing to speculate that a substance from outside causes PD**

**For this reason we have developed an animal model and could demonstrate that this model is in perfect agreement with Braak‘s staging**

**Gut microbiota may play an important role in the progression of PD and further work is needed to check whether the use of probiotics is helpful**

# Thank you for your kind interest

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